FDA Lead Reviewer Summary

W.L. GORE & Associates
EXCLUDER Bifurcated Endoprosthesis

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September 9, 2002, Circulatory System Devices Panel Meeting

Introduction

- **This presentation will include the following:**
  - **an introduction of the review team;**
  - **a summary of the FDA review; and**
  - **the questions for panel consideration.**
- **The sponsor's presentations from this morning accurately summarize the data reviewed by the agency, so these data will not be repeated in this presentation.**

Review Team

Lead Clinical	**Paul Chandeysson, M.D.**
Adjunctive Clinical	**Julie Swain, M.D.**
Statistical	**Gary Kamer**
In Vivo - Animal Studies	**John Karanian, Ph.D.**
In Vitro:	
Delivery System	**Kachi Enyinna**
Graft Mechanical Testing	**Terry Woods, Ph.D.**
Graft Corrosion Testing	**Stan Brown, Ph.D.**

Review Team

Biocompatibility, Packaging and Sterilization	Lisa Kennell
Bioresearch Monitoring	Barbara Crowl
Manufacturing/QSR	Mary Jo Scott
Patient Labeling	Walter Scott, Ph.D.

FDA Review Summary

Pre-clinical

- **FDA reviews of the biocompatibility, *in vivo* animal studies, manufacturing and sterilization information (including packaging and shelf-life) have been completed. There are no issues regarding these areas for the panel to discuss.**

Device Integrity

- **FDA review included assessment of device integrity.**
- **As with other stents used in the vascular system, endovascular grafts may be subject to conditions which may result in loss of device integrity.**

Device Integrity

- **Depending upon location and type of the breach in integrity, there may or may not be an immediate or eventual clinical consequence.**
- **Another factor which must be considered in the review of this issue is the difficulty in identifying and confirming the presence of structural failures *in vivo*.**

Device Integrity

- **Prior to sending the panel packs out for review, there were two reports of wire-form fractures identified by the Core Laboratory, one at discharge in a patient enrolled in the Phase II study, and the other at 12 months in a patient enrolled in the ongoing second generation device study.**

Device Integrity

- **Upon learning of these reports, the sponsor conducted a failure analysis and communicated their findings to the FDA.**
- **There have been no adverse events associated with either report.**
- **There is not conclusive evidence to verify the presence or absence of the fractures.**

Device Integrity

- **Both reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta.**
- **The FDA review of the failure analysis of these two reports has been completed, with no additional information requested of the sponsor.**

Device Integrity

- **The sponsor recently reported a fracture identified in an explanted device. The fracture was in the bifurcated region of the device. Limited information is available at this time.**

Clinical Study History

Protocol		Enrollment Period	# of Sites	# of Patients	
				Device	Control
Feasibility Study	Registry	Jan 1998 - Oct 1998	3	29	--
Pivotal Study	Study device compared to concurrent open surgical control, i.e., pts. unable to receive EBE	Dec 1998 - Jan. 2000	19	235	99
Continued access	Registry with the same follow-up as for the pivotal study	Nov 1999 – Apr 2000	6	49	--
Emergency Use	Follow-up at the discretion of the investigator		3	3	--

Clinical

- **Notable issues the sponsor addressed regarding the clinical data included:**
  - **the appropriateness of the non-randomized study design;**
  - **difficulty in enrolling women;**
  - **the number of, reasons for, and outcome of patients converted to open surgical repair;**
  - **clarification of the rate of major adverse events after 1 month; and**
  - **clarification of the number of type I & III endoleaks and aneurysm enlargements.**

FDA Review Summary

- **All FDA requests for additional information have been satisfied.**
- **The review team identified the following questions for the panel to discuss.**

FDA Questions for the Panel

1. **The primary safety endpoint of the clinical study was the rate of major complications as evaluated through 12 months. Additionally, data are presented for individual adverse events, analyses are provided for risk factors associated with adverse events, and causes of death are provided. A summary of the 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of safety in the intended population.**

FDA Questions for the Panel

2. **The primary effectiveness endpoint of the clinical study was exclusion of the infrarenal abdominal aortic aneurysm from the blood circulation, defined by absence of aneurysm enlargement and endoleaks, as evaluated through 12 months. Additionally, data regarding potential problems associated with endovascular treatment (e.g., migration, aneurysm enlargement, endoleaks, ruptures, conversion, device integrity) are presented. A summary of the 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of effectiveness in the intended population.**

FDA Questions for the Panel

3. **The Core Laboratory has reported two cases of wire-form fractures, one identified at discharge in a patient enrolled in the pivotal clinical study, and the other at 12 months in a patient enrolled in the ongoing second generation device study. There have been no adverse events associated with either report, and there is not conclusive evidence to verify the presence or absence of the fractures. Both reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta.**

FDA Questions for the Panel

3. (cont.) After the panel packs were sent to the Panel, the sponsor reported a wire-form fracture which was recently identified during the sponsor's analysis of a device explanted in Germany. Details concerning the length of implantation, implanting physician identity, and device lot and serial numbers remain unavailable. Based on the sponsor's analysis it appears that the fracture, which was also located in the main body of the graft in the crotch of the bifurcation, did not result in any clinical complications and the ends of the wire did not appear to be protruding through the device material or the surrounding tissue. **Please comment on the significance of these observations.**

FDA Questions for the Panel

4. One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events.

FDA Questions for the Panel

4.(a) **Does the INDICATION FOR USE, as stated below, adequately define the patient population studied, and for which the device will be marketed?**

"The EXCLUDER Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal AAA disease who have appropriate anatomy."

FDA Questions for the Panel

4.(b) Based on the clinical investigation experience, are there any additional warnings, precautions, or contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts?

FDA Questions for the Panel

4.(c) Please comment on whether the instructions for use adequately describe how the device is to be delivered.

FDA Questions for the Panel

4.(d) Do you have any other comments on the labeling?

FDA Questions for the Panel

5. **Please comment on the adequacy of the proposed physician training plan, as described in the panel package.**

FDA Questions for the Panel

6. **The sponsor is proposing to conduct a post-approval study on the patients enrolled in the pivotal clinical study (i.e., 235 test patients and 99 controls). Five-year follow-up on all patients who are alive and not withdrawn from the study will be obtained in accordance with the clinical protocol approved under the IDE for this device. Please comment on the acceptability of this plan, as briefly described in the panel package.**

Panel Discussion